Kicking in infants with perinatal stroke: can we predict ability and disability?

Honors Thesis

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Abstract Stroke in very young infants is the most common cause of cerebral palsy, a chronic disorder of motor function impairments with lifetime physical, social, and emotional consequences. While stroke is typically diagnosed within the first week of life, cerebral palsy is diagnosed much later, at 18-24 months of age. Spontaneous kicking is one of the few early movements that has been shown to be indicative of motor ability in young infants with motor disorders. This is a longitudinal trial of children 2.5-7.5 months describing spontaneous kick quantity and quality in infants with and without stroke and those who go on to have CP. Infants were tested in 2 conditions: with and without toys. N=29 infants completed this study (n=11 with perinatal stroke (PS); n=18 typically developing (TD)). Medical chart review at 3 years of age determined cerebral palsy status of infants with stroke. Infants were videotaped kicking freely for eight, thirty-second trials, six with toys, two without. Videos were then analyzed by two trained blinded raters with overall agreement of 0.96. Infants with cerebral palsy showed a statistical interaction with infants without cerebral palsy for total kicks ($p=0.019$) and two of three kick subtypes ($p=0.041$; $p=0.029$). The no toy condition yielded more kicks than the toy condition for total kicks ($p=0.025$) and two of three kick subtypes ($p=0.050$; $p=0.065$). Our findings support the possibility that spontaneous kicking may be used to identify infants with motor deficits at much younger ages than is currently possible. The use of toys in lower extremity analyses is cautioned.

I. Proposal

Problem Statement Infants with perinatal stroke (PS) are at risk for developing cerebral palsy (CP). Clinical diagnosis of CP is often not possible until 18-24 months of age, after a critical window for interventional therapy has been missed. While emerging assessment methods have successfully predicted CP from as early as 3 weeks, they often exclude lower extremity (LE) analysis. A diagnostic measure for LE impairment in infants with PS is needed.

Introduction When thinking about strokes, rarely does the infant population come to mind. Yet the incidence of stroke in neonates in second only to the elderly, and children are at their highest risk for stroke during the perinatal period (Raju et al., 2007). Described as a disruption in cerebral blood flow between 22 weeks gestational age and the first week of life, a perinatal stroke (PS) occurs between 1 in 1600 and 5000 live births (Cioni et al., 2011; Lynch et al., 2009). Like their adult counterparts, infant strokes can be ischemic, in which a blockage in the blood vessel restricts blood flow to the brain, or hemorrhagic, where weakened blood vessels rupture and bleed into the surrounding tissue (Riel-Romero et al., 2008). Although the causes of PS are not fully understood, a number of risk factors have been identified including dehydration, birth asphyxia, central nervous system infection, autoimmune disorders, and congenital heart disease, among others (Nelson & Lynch 2004). The primary indicator of a stroke is the presence of seizures, although other symptoms, especially in the case of neonates, may take weeks or even years to manifest. Strokes are typically diagnosed by MRI, although some are diagnosed retrospectively (Nelson & Lynch 2004).

One of the more interesting aspects of studying lesions in developing brains is the principle of neuroplasticity. During gestation and early infancy neurons proliferate and actively migrate throughout the brain to form set pathways. When the migration is blocked or disrupted, as in the case of a stroke, the infant brain has shown incredible initiative in adapting and reorganizing neural pathways in order to retain functionality (Fiori et al., 2015b). The now famous Kennard Principle says it most succinctly: if you’re going to have brain damage, have it early (Dennis et al., 2010).

The intricacies and limitations of plasticity are especially evident when studying motor functionality. In the adult brain, the motor cortices are related to the body via contralateral connections, i.e. the right motor cortex initiates movement in the left side of the body. In adults impacted by stroke a reduction in motor capabilities is often immediately evident contralateral to the lesion, and indeed serves as one of the primary indicators of adult stroke. With congenital lesions a contralateral hemiplegia is also often seen, but the mechanisms underlying it are more complex (Fiori et al., 2015b). It had been shown via transcranial magnetic stimulation, fMRI, and post-mortem analysis that not only do contralateral pathways exist in the developing brain, but also ipsilateral (same-side) projections (Fiori et al., 2015a; Staudt et al., 2004). Competition between hemispheres typically results in the withdrawal of the ipsilateral pathways (Fiori et al., 2015b). When the hemispheric competition is reduced or missing entirely, as could be the case with stroke, it has been determined that the ipsilateral path is able to proliferate and competitively displace contralateral projections from the affected hemisphere. Effectively, this results in the unaffected motor cortex assuming responsibility for both sides of the body (Eyre et al., 2007). The basal ganglia has also been shown to have ipsilateral capability, while the somatosensory cortex typically remains in the affected hemisphere (Juenger et al., 2008). Ipsilateral retention usually occurs when significant damage has occurred in the affected hemisphere (Fiori et al., 2015a). This typically results in some degree of motor reduction in the ipsilateral, or contralesional, hand, but good or even typical control can be achieved (Staudt et al., 2004). In one case study, hand control was so good that the presence of an ipsilateral pathway was only suggested by the presence of mirror movements and confirmed by transcranial magnetic stimulation (Fiori et al., 2015a).

While an exciting phenomenon, plasticity is not always as straightforward or beneficial as we would like. Cases where plasticity resulted in adverse effects have been termed “maladaptive plasticity” and can have serious impact. Whether ipsilateral projections are beneficial remains up to debate. While good outcomes have been noted, others posit that displacement of the natural contralateral projections, even weakened or damaged ones, may aggravate long-term impairment (Eyre et al., 2007). The fact that the somatosensory cortex rarely migrates hemispheres, and therefore is disconnected from the corresponding motor cortex, lends some credence to this theory. More inquiry is needed at this time.

Plasticity is affected by a variety of factors. Concerning congenital lesions, the highest impactors are lesion distribution and timing (Fiori et al., 2015b). Distribution may seem self-explanatory, but there is also increasing evidence that plasticity decreases significantly even over the course of gestation. It has been widely noted that the closer to term a stroke occurs, the more significant the damage, but whether this is due to decreased plasticity, the nature of late-term strokes, or some combination of the two remains to be determined. During the first and second trimesters cerebral morphogenesis and neuronal migration are most pronounced, and strokes during this period typically result in adaptive brain malformations. In contrast, third trimester strokes usually result in gliotic and cystic defects and can be further divided into “early third” lesions, which tend to affect white matter, and “late third” trimester or perinatal lesions, which typically affect gray matter (Staudt 2004). A clear difference in outcomes can be found even between these three groups. In patients with congenital hemiparesis Staudt *et al.* found a significant inverse relationship between timing of lesion and paretic hand motor scores, with earlier lesions resulting in better scores. Subjects were then separated according to contralateral or ipsilateral control. In both groups early lesion patients significantly outperformed the early third group, who outperformed the late third group; in addition, late lesion patients with ipsilateral projections exhibited little to no control of the paretic hand (Staudt et al., 2004). This suggests that, when necessary, early lesion patients were able to successfully shift motor control to the unaffected side. Since by the third trimester neuronal migration is largely finished, it follows that lesions occurring later in gestation are not as successful in remedying damage (Cioni et al., 2011).

Taken together, the literature suggests that large lesions that occur early in gestation in the motor cortex or basal ganglia will result in shifting, while small lesions occurring in the somatosensory cortex late in gestation will not. While motor shifting does not necessarily correlate with a better outcome, lesion analysis should prove relevant for the current project.

A related topic of interest is that of mirroring. Mirror movements refer to "simultaneous contralateral, involuntary, identical movements that accompany voluntary movements" and occur primarily with distal upper extremity movements. Mirror movements are associated with several severe neurologic conditions, including cerebral palsy. Farmer et al. concluded that the impulse that produces both voluntary and mirrored movement arises from a single source (1990). This has given rise to the popular theory that mirroring is a result of a atypical branched neuronal pathway between the motor cortex and hands, and in 2002 Staudt demonstrated that mirror movements are strongly associated to an ipsilateral relationship between active motor cortex and paretic hand. However, when mirror movements were divided into paretic hand (movements in unaffected hand producing mirrors in paretic hand) and unaffected hand, only mirror movements in the paretic hand were found to be indicative of ipsilateral connectivity (Staudt et al., 2004). Furthermore, unaffected hand mirror movements are consistent with mirroring seen in adults stroke patients. Since adults are expected to retain a contralateral relationship with the lesional hemisphere, this consistency suggests that, at least for contralateral patients, another explanation may exist. Staudt suggests that this may be due to a motor "overflow" phenomenon, which has been described in patients with significant motor impairment (Staudt 2004). Infants typically exhibit difficulty dissociating movements between limbs (Nadkarni 2012). It may be possible to distinguish typical behavior from true mirroring, however, and the current project will pay close attention to bilateral movements.

While perinatal patients show incredible capacity for endogenous rehabilitation, impairment and disability in populations with PS is still quite common. In total, 25% of all developmental disability can be attributed to perinatal brain injury (Cioni et al., 2011). Hemiplegia, in which one side of the body is weaker than the other, will affect most infants with PS. PS has also been identified as the most common cause of hemiplegic cerebral palsy (CP), a disorder of movement, tone, or posture characterized by poor muscle strength, decreased joint range of motion, muscle spasticity, and poor dexterity (Klingels et al, 2012). Some studies have suggested that 30% of infants affected by PS will experience impaired motor development, with the majority of those developing CP (Husson et al., 2014). Ischemic stroke in neonates is responsible for 50-70% of all cases of congenital cerebral palsy (Lee et al., 2005).

Measures have been developed to predict the incidence of CP in high risk populations in the earliest stages of life. MRI taken during the first week of life is predictive of CP development. Specifically, pre-Wallerian degeneration and lesions of the basal ganglia or thalamus have been proven useful in CP prediction (Vries et al., 2011). However, it has been suggested that MRI taken on or before postnatal day 4 may overestimate damage (Ferrari et al., 2011). Predictive power of early imaging is enhanced when sequential cranial ultrasonography is utilized, and some have suggested that serial imaging can even indicate severity of CP (Vries et al., 2011). However, neonatal outcome has continued to improve in wake of recent developments. Therapeutic hypothermia has especially improved outcomes, to the point that the specific efficacy of imaging is less clear (Vries et al., 2011). Other early-life predictors of CP include higher gestational age of incident, asphyxia, deep gray matter lesions, among others (Himpens et al., 2010).

Although early EEG and MRI may predict which infants will develop hemiplegia, additional measures are needed. In adults motor impairment is typically diagnosed by the presence of a sharp drop in motor capability associated with a sudden neurological event. Perinatal stroke, however, occurs so early in life that infants have not yet established a standard of motor control. Additionally, the low muscle tone and poor coordination universally exhibited by infants means that gross motor control is difficult to assess. In typical clinical practice children are not diagnosed with motor impairment and referred to treatment until 18-24 months of age, after a series of critical motor milestones have been missed (Guzzetta 2003). The prolonged period of time between which an infant suffers a stroke and when they begin to receive treatment represents a window of opportunity in which interventional therapy can be critical.

The neurological basis for early intervention is clear. Neuronal differentiation continues for several months after birth, and the maturation of dendrites and axons continues through the first eight months of life (Hadders-Algra 2004; Cioni et al., 2011). In addition, approximately half of newly generated neurons will undergo apoptosis (Hadders-Algra 2004). The popular theoretical understanding of which neurons survive states that new neurons depend on enrichment for survival, or "experience-dependent neuroplasticity" (Vaccarino & Ment 2004; Cioni et al., 2011). In even the youngest infants it has been hypothesized that brain maturation can be guided by environment enrichment, including social and sensory experiences, as well as the reduction of stress (Cioni et al., 2011). When applied to infants with stroke, early intervention becomes especially important. Activation of the damaged corticospinal system may be critical in preventing neuronal apoptosis and further impairment of motor capability. In addition, continuing plasticity between the sensorimotor cortex and displaced motor cortex "strongly support early intervention" (Cioni et al., 2011). As Hadders-Algra put it, “The neuronal elements that fit the environment best persist”, and early intervention may be key to ensuring that motor neurons are the ones persisting (2004).

A popular question from those that haven't worked with infants before is whether intervention can be effective so early in life. Specific therapeutic measures has shown to be successful in infants and young children at risk for motor impairment. CP patients as young as 1 year showed marked improvement in muscular tone and locomotor activity after umbilical cord blood cell transfusions (Romanov et al., 2015). Tactile massage has been shown to increase weight gain in premature imfants (Diego et al., 2014). Typically, the bulk of intervention involves physical therapy. Head control therapy has been shown to hasten emergence of controlled head movements (Lee et al., 2012). Exercise training increased weight absorption, bone formation, and circulating leptin in premature infants (Diego et al., 2014; Nemet et al, 2002; Vignochi et al., 2012; Eliakim et al., 2002). Caregiver-based daily movement training was shown to facilitate reaching in premature infants (Heathcock et al., 2007). As a low-cost, noninvasive strategy, physical therapy has also been shown to have high rates of compliance. In one study, parents of premature infants were found to have 96% compliance with therapy visits during the transition from the NICU to home (Dusing et al., 2015).

However, early intervention cannot be utilized without reliable, early diagnoses. In order to close the gap between the age at which a stroke is diagnosed (7 days) and the age at which CP can be diagnosed (18 months), a new method of measuring movement in very young infants must be developed. It has been widely noted that very young infants do not exhibit directed, purposeful movements. That is not to say, however, that infants don't move. Barlow & Estep noted that a variety of "spontaneous rhythmic movements" were present in embryos and neonates well before they were needed for behavior (2006). Many of these movements are quite complex and include a level of coordination far above what would be expected for perinatal movement. Their existence can be attributed to the presence of central pattern generators, which are neuronal networks that have the information necessary to generate motor patterns (Barlowe & Estep 2006). In young infants, the produced motor patterns are spontaneous in nature and may be repeated thousands of times in a single day. Importantly, these early movements are distinctive and measurable and have been shown to be related to motor impairment. Einspieler & Prechtl noted that when the nervous system is impaired, a clear reduction in spontaneous movement variability and complexity can be noticed (Einspieler & Prechtl 2005). Asymmetries in upper extremity movements were found to be indicative of hemiplegia from as early as 3-6 weeks (Guzzetta 2010). One particular type of early spontaneous movements, general movements, have been shown to have predictive power similar to neuroimaging and better than neurological examination (Soleimani et al., 2015; Cioni et al., 1997). It has also been noted that spontaneous movements evaluation is especially cost-effective and non-intrusive, and thus is of special interest to developing and low-technology countries where MRI and other imaging is not readily available (Soleimani et al., 2015). From what we have seen, we propose that spontaneous movement evaluation is a promising method of movement analysis in very young infants.

In addition, we believe that the lower extremities (LE) should be an area of interest in CP diagnosis. In children with CP the upper extremity is more affected than the lower extremity, leading most studies to exclude LE analysis (Damiano et al., 2006). There is evidence, however, that LEs can be very useful in predicting outcomes. Qualitative analysis of LE function may be predictive of di- and tetraplegia as early as 1-3 months (van der Heide 1999). At 9-20 weeks, infants exhibiting no leg movements were at risk for bilateral and dyskinetic CP (Yang et al., 2012). LE deficits may also be predictive of spastic hemiplegia at 2-8 months (Yokochi et al., 1995). The addition of LE parameters may facilitate accurate diagnosis of tetraplegia, hemiplegia, and diplegia of the legs.

The specific lower extremity movement most studied in early infancy is spontaneous kicking. This is in part due to the fact that spontaneous kicks appear at the earliest stages of life, being commonly seen in-utero. They have been studied in many infant populations at risk for neurological deficits. Infants with spina bifida were found to demonstrate a noticeable decrease in kick quantity compared to their typical peers, while infants with Down Syndrome maintained similar quantity but decreased quality (Chapman 2002; Ulrich et al., 1995). Preterm infants initially demonstrated a much higher kick rate, but at 12 weeks sharply decreased kicks to a level comparable to typical infants (Geerdink et al., 1996). Monotonous kicking patterns were associated with "severe functional limitations" in school age children. The total absence of kicking in combination with cramped-synchronized movements is also indicative of CP (Bruggink et al., 2009). To our knowledge this is the only study relating spontaneous kicking to CP. A preliminary analysis of our population revealed that a large majority of infants with PS will exhibit some degree of kicking, leading us to conclude that further research in this area is necessary. In addition, the wide variety of kicking behaviors demonstrated by at-risk infants leads us to believe that behavior may be related to specific neurological condition rather than a broad state of motor impairment. This theory is echoed by several other researchers. Heriza posits that differences in behavior can be attributed to "dynamic interaction of elements in the motor control system" (1988). Geerdink *et al.* found that kicking differences were not at all related to items such as leg volume and posture control, but rather neurological condition (1996). The literature leads us to believe that infants with PS will exhibit an identifiable, condition-specific kicking pattern.

Kicking behaviors for typical infants have been defined. A peak in kick frequency is expected around 8 weeks of age (Jeng et al., 2004). Three distinct kick types have been identified. Unilateral occurs when one leg kicks without corresponding movement from the other. It has been noted that unilateral kicks most closely resemble mature walking (Thelen et al., 1983). Parallel kicks, in which both legs kick simultaneously, have been identified as the most difficult and mature kick type. Their frequency is often used to define quality measures (Jeng et al., 2004). The last type, alternating, occurs when a kick from one leg is followed immediately by a kick from the other. Alternating kicks are widely considered the most immature type, and a significant decrease in the percentage of alternating kicks is expected beginning at 4 weeks (Thelen et al., 1983).

There is also increasing evidence that spontaneous kicks are predictive of crawling and kicking onset. Thelen *et al.* first reported that the overall spatial pattern of spontaneous kicks closely resembles that of a walking adult in 1981. More recently, kick frequency was found to be significantly associated with crawling and walking onset at 22 weeks (Ulrich & Ulrich 1995). Delayed walkers exhibited differences in kick frequency and quality (Jeng et al., 2004). Van der Heide *et al*., however, found no correlation between the presence of brain lesions in preterm infants and kick frequency. In addition, asymmetries in LE movements have been difficult to identify (Yokochi 1995). These findings are important in light of the fact that failure to walk by 18 months is strongly associated with neurodevelopmental disorders (Jeng et al., 2004). The lack of LE parameters is especially surprising considering children with hemiplegic CP often demonstrate asymmetric gait impairment (Myens et al., 2012). In addition, targeted kicking therapy has demonstrated improvements in LE performance in children at risk for CP, which further emphasizes the need for early identification of LE deficits (Campbell et al., 2012).

A further topic of interest to the researchers is the impact of toys on spontaneous kicking. The use of toys is nearly ubiquitous in clinical evaluation of infants as a form of communication and way of eliciting specific behaviors. Bright colors, varied textures, and sounds are considered especially stimulating for infants (Gunner et al., 2005). Their impact on LE function, however, has not been clearly defined. Toy-oriented movement training increases purposeful leg movements in preterm infants (Heathcock et al., 2009). Similarly, Bruner *et al.* found that the use of a toy that “reacts” to a target movement will facilitate sustainable growth in mean target responses. The same study, however, found that a nonreactive toy had no impact on responses (Bruner et al., 1976). In addition, Ulrich & Ulrich found that infants sharply decreased their spontaneous kicking frequency when engaged with a randomly moving mobile when compared to verbal engagement. The study also suggested that infants at 15 weeks were much more likely to modify their kick frequency according to engagement than at 22 weeks (Ulrich & Ulrich1995). Taken together, the literature suggests that while toys may be useful in encouraging spontaneous movements, the method of toy presentation and interaction is more important than the toy itself.

Objectives

(1) To examine the relationship between spontaneous kicking quantity and quality and the development of cerebral palsy in PS infants. We hypothesize that PS infants who will go on to develop cerebral palsy will show differences in kick quantity and quality compared to peers who will not develop cerebral palsy;

(2) To examine the impact of toys on spontaneous kicking quantity and quality. We hypothesize that the toy condition will elicit greater kick quantity and quality than the no toy condition.

Methods

Participants. N=29 infants completed this study (*n*=11 infants with stroke, PS; *n*=18 typically developing, TD) Inclusion criteria were gestational age at birth of >37 weeks and stroke for the PS group. TD were reported as typical by a primary caregiver. Exclusion criteria included genetic or metabolic disorders and orthopedic impairments that may affect kicking behavior. Infants with PS were recruited from the Stroke Clinic at Nationwide Children's Hospital in Columbus, Ohio. PS diagnosis was confirmed by magnetic resonance imaging and read by a pediatric neurologist. At 3 years of age a medical chart review of infants with PS was conducted to determine cerebral palsy status. Of the eleven infants, three, or 27%, were found to have developed cerebral palsy and are designated as CP. Eight were found to not have developed cerebral palsy and are designated PS n. Infants began the study at approximately 2.5 months of age in both the TD group (*n*=18, 10 boys, 8 girls, mean age=10.80 ± 0.95 weeks) and PS group (*n*=11, 8 boys, 3 girls, mean age=10.13 ± 1.42 weeks). This study was approved by Nationwide Children's Hospital and The Ohio State University Research Institution Review Board (IRB). Informed consent was obtained from one parent before data collection.

Procedure. Data collections occurred at the Infant Biomechanics Lab in Columbus, Ohio. Infants were seen every other week from 2.5 to 7.5 months of age for ten sessions. Infants were laid supine and allowed to kick freely for eight, thirty-seconds trials. For six of the trials infants held toys and for two trials no toys were present. Three different toys were used individually for two trials each, and trials were collapsed after preliminary analysis revealed no significant differences in kicking between toys. Trials were filmed on a digital video camera at 30 frames per second. A kick was defined as the flexion or extension of both the hip and knee of at least ten degrees with recoil in the opposite direction within one second. Kicks were then divided into unilateral, parallel, and alternating kicks. A unilateral kick is defined as a kick from only one leg and is considered baseline quality. A parallel kick occurs when both legs kick in synchrony for at least 50% of the kick and is considered the most coordinated, and thus highest quality, kick type. An alternating kick occurs when a kick from one leg is followed immediately by a kick from the other. Alternating kicks are typically seen in less mature infants and are thus defined as the least quality kick type. Total kicks is the sum of unilateral, parallel, and alternating kicks. Kick *quantity* was determined by the frequency of total and unilateral kicks, and kick *quality* was determined by the frequency of alternating and parallel kicks. Frequency was the mean number of kicks per trial for a session.

Behavioral Coding and Data Management. Videos were analyzed by two trained raters with overall agreement of 0.96 on 10% of trials by ICC. Raters were blinded to group assignment. Sessions 7-10 were excluded from the study as many infants had begun to roll over.

Statistical Analysis. IBM SPSS 23.0 software was used for statistical analysis. Repeated measures multivariate ANOVAs (2 or 3 group × 6 session) were used to identify the relationships between within-subject effects (time) and between-subject effects (group) to kick frequency. A repeated measures ANOVA (2 condition× 6 session) with within-subject designs were used for toy and no toy comparison. A *p*-value <0.05 was defined significant.

Preliminary Results Results from the first 6 visits are reported here.

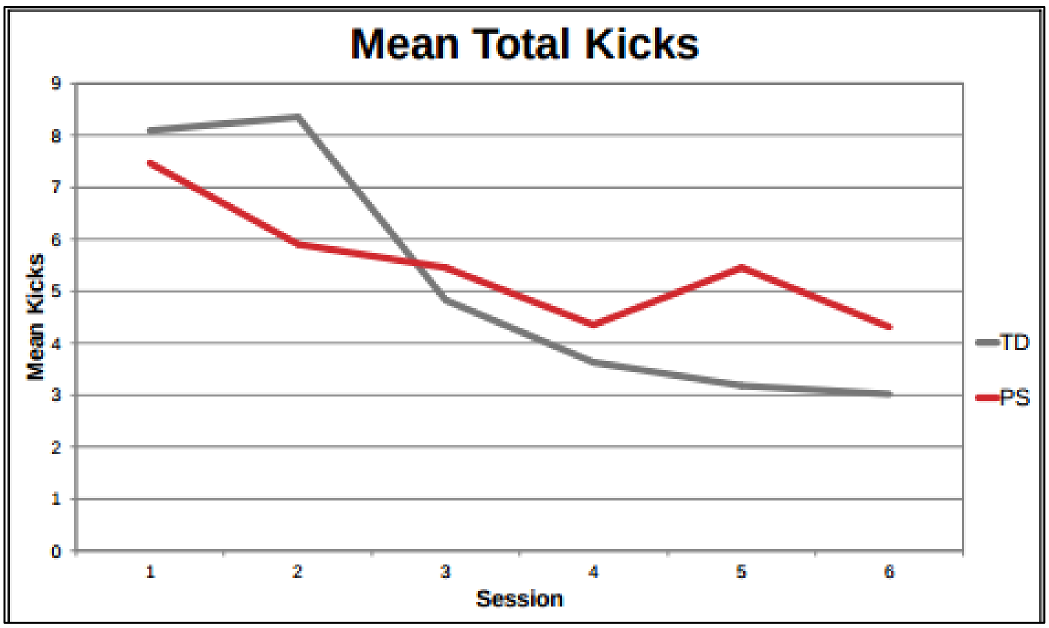
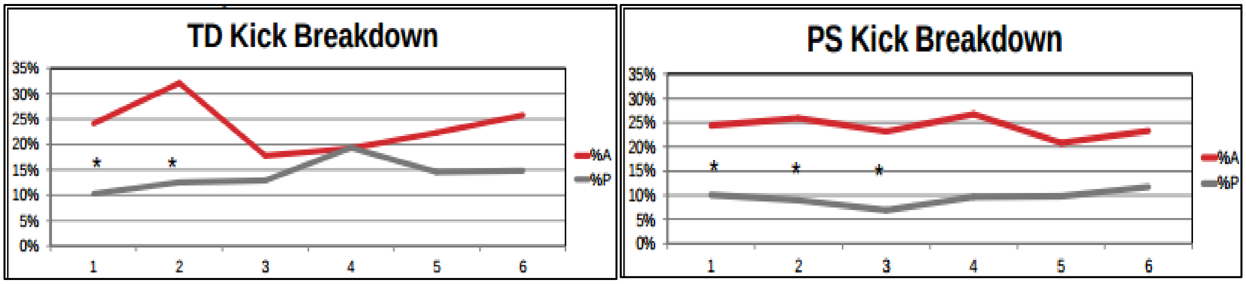


Figure 1. Mean total kicks over 6 visits for TD (grey) and PS (red) infants. Differences in kick quantity are most notable at visits 2 and 5. A 2 (group) x 6 (session) repeated measures AVOVA revealed a main effect for time, which means that all infants decreased their kicks over time. Further analysis will be needed to determine if individual infants are the source of the difference. The literature suggests that typical infants will decrease their kicks over time.



Figures 2 & 3. The relative percentages of two kick subtypes (P=parallel, A=alternating) is shown for TD (2) and PS (3) infants. Alternating kicks have been identified as the least mature kick subtype and are significantly more prevalent than parallel kicks for both TD and PS infants at session 1. As an infant matures their kick quality, it is expected that the difference between alternating and parallel kicks will become insignificant. Again, this occurred for both groups, but at different rates. TD infants showed an increase in kick quality in 2 visits, where PS infants took 3 visits and still show substantial (but not significant) separation between alternating and parallel kicks beyond this point.

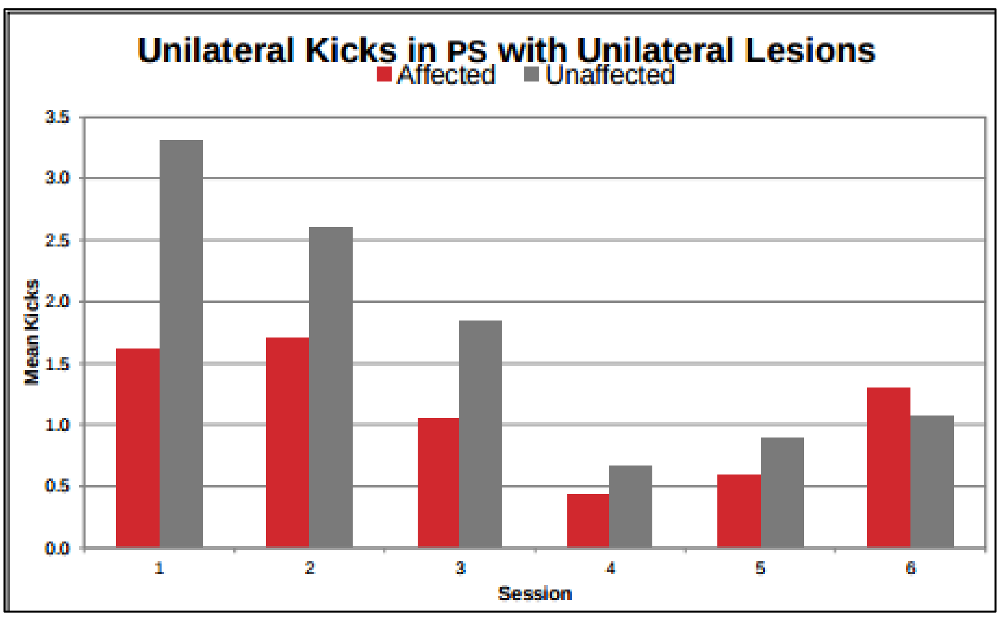


Figure 4. Infants with unilateral lesions were examined for the unilateral kick subtype, which is the only kick type involving only one leg. Due to the contralateral relationship of the motor cortices with the body, a unilateral lesion is expected to impact only one hemisphere of the body. Kicks were therefore divided into affected and unaffected sides. In visits 1-3, kicks from the unaffected side seem to be much more prevalent than affected side kicks. It is important to note, however, that only 6 infants met the criteria to be included in the analysis.

Preliminary Discussion At this time, differences in spontaneous kicking may be detectable between typically developing infants and infants with perinatal stroke. Especially promising results have been noted in the area of kick quality, where the relative percentages of alternating and parallel kicks may reveal differences. In addition, separating kicks in PS infants into affected and unaffected sides may be useful. Since asymmetry is expected in children with hemiplegic cerebral palsy, affected side kicking performance may serve as a primary indicator of CP. At this time, however, statistical analysis has revealed the need for more infants in order to increase in study's power.

The next steps for the study include establishing typical kicking trajectories and then identifying abnormal kicking patterns. Standard deviations will be calculated and abnormalities in terms of kick rate and relative percentages will be scrutinized. While we expect to see wide variability in both of these measures, the literature leads us to believe that infants who will go on to develop CP will exhibit a distinct kicking pattern. Identifying this pattern, predicting the infants who will develop CP, and then comparing these predictions to actual outcomes to measure accuracy will compose the bulk of this thesis. If we are incorrect in our predictions, we will retrospectively analyze the affected infants' patterns.

Further steps include analyzing corresponding clinical variables. Further lesion analysis can reveal size and lesion type, which may indicate the gestational age of the infant when the lesion occurred. This will allow us to compare the efficacy of spontaneous kicking in predicting CP in comparison to the traditional MRI, which will help determine whether spontaneous kicking can be a useful and appropriate tool in clinical diagnosis of CP.

II. Defense

Results There was no difference in age between groups at the first visit (p=0.183). TD and PS infant kicking was analyzed with a repeated measures multivariate ANOVA (2 group × 6 session), revealing no difference in kick quantity or quality. A main effect of time was found to be significant for total kicks ($F(2,140)=3.854$, $p=0.007$) and unilateral kicks ($F(2,140)=6.009$, $p<0.001$) with a trend towards effect of time found for alternating kicks ($F(2,140)=2.245$, $p=0.077$). This indicates that as a group, infants decreased their kicking across the study period and that infants with PS are not distinguishable from TD infants using spontaneous kick quantity or quality alone.

At 3 years PS infants were designated to have cerebral palsy (CP, n=3, 1 male, 2 females, age=8.95 ± 0.66 weeks) or no cerebral palsy (PS_n, n=8, 7 males, 1 female, age=10.57 ± 1.39 weeks). PS outcomes of no cerebral palsy (PS_n) and cerebral palsy (CP) are indicated.

Table 1. Characteristics of PS Infants.

Subject	Outcome	Gender	Age at first visit (days)	Main Injury Type
1	PS_n	M	62	Ischemia
2	PS_n	F	87	Cerebellar Hemorrhage
3	PS_n	M	72	*Unclassified*
4	PS_n	M	63	Venous Infarction
5	PS_n	M	84	Diffuse White Matter Injury
6	PS_n	M	66	Intracranial Hemorrhage
7	PS_n	M	77	Intracranial Hemorrhage
8	PS_n	M	81	Venous Infarction
9	CP	F	60	Venous Infarction
10	CP	F	68	Bilateral Hemorrhage
11	CP	M	60	Cerebral Infarction

Note: PS: perinatal stroke; PS_n: perinatal stroke infant who does not develop cerebral palsy; CP: perinatal stroke infant who does develop cerebral palsy.

A multivariate repeated measures ANOVA (3 group × 6 session) revealed a significant interaction between TD, PS_n, and CP for total kicks ($F(3,140)=2.249$, $p=0.019$), unilateral kicks ($F(3,140)=2.149$, $p=0.041$), and alternating kicks ($F(3,140)=2.373$, $p=0.029$), indicating that at least one group displayed a significantly different trajectory from the rest. No main effect of time was found.

A multivariate repeated measures ANOVA (2 group × 6 session) performed for PS_n and CP alone revealed significant interactions for total kicks ($F(2,140)=3.375$, $p=0.011$), unilateral kicks ($F(2,140)=3.535$, $p=0.009$), and alternating kicks ($F(2,140)=3.182$, $p=0.015$), indicating that infants with CP were distinguishable for kick quantity and one measure of kick quality from PS_n infants. Similar interactions were found between CP and TD. No interaction was found between TD and PS_n.

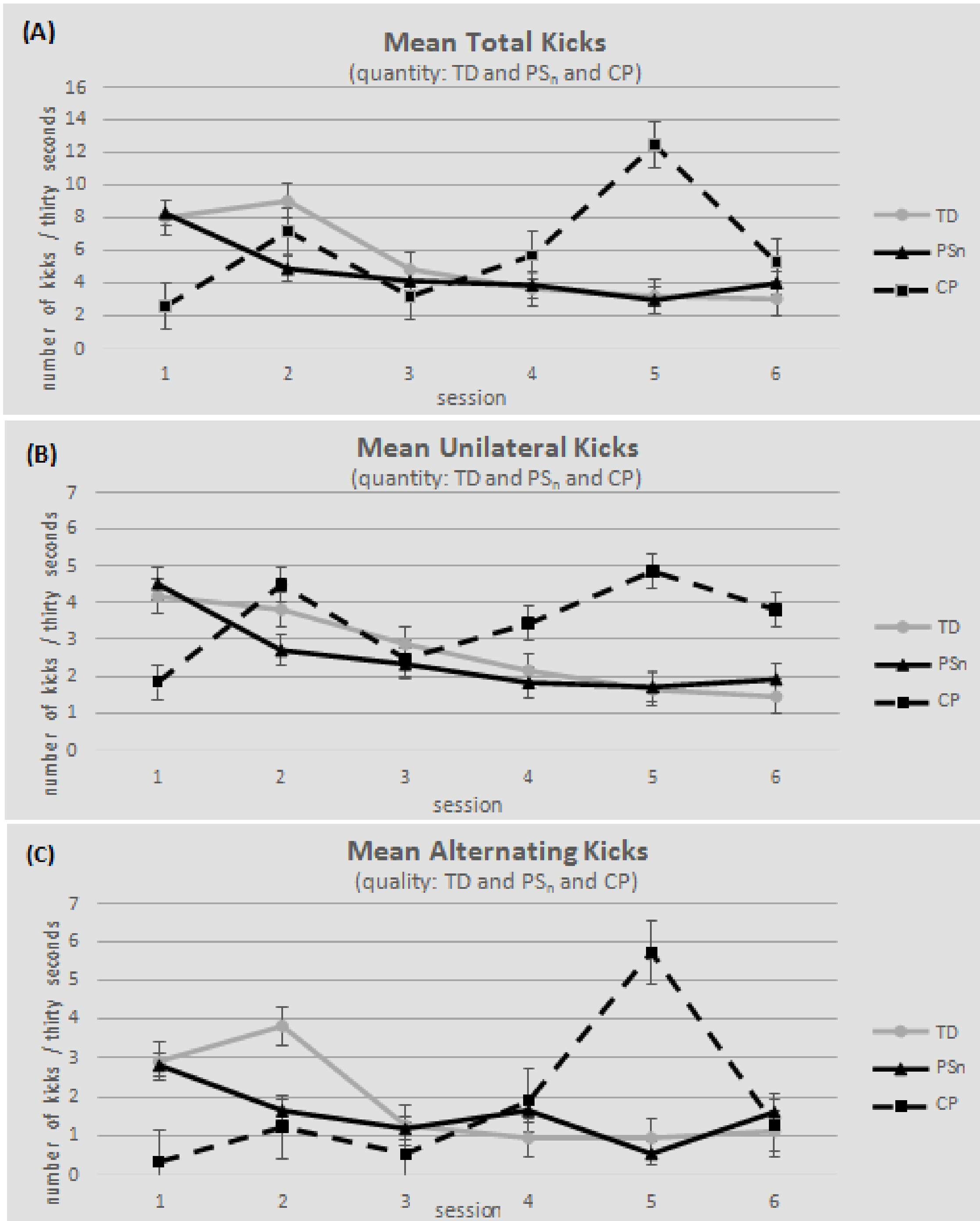


Figure 2. Kicking rate for TD, PS_n, and CP infants for (A) total kicks; (B) unilateral kicks; (C) alternating kicks. *Note*: TD: typically developing; PS_n: perinatal stroke infant who does not develop cerebral palsy; CP: perinatal stroke infant who develops cerebral palsy. One session = two weeks.

Kicking performance with and without toys was then investigated. Two TD infants and two infants with PS lacked no toy condition data and were excluded to yield N=24. Trials were divided into conditions with toys (TOY) and without toys (NTY). A repeated measures ANOVA (2 condition × 6 session) with within-subject designs was used for TOY and NTY comparison. A significant effect for toy was found for total ($F(2,23)=5.77$, $p=0.025$) and unilateral kicks ($F(2,23)=4.283$, $p=0.050$) and a trend for toy effect for parallel kicks ($F(2,23)=3.779$, $p=0.065$). This indicated that the no toy condition facilitated more kicks than the toy condition. No interaction was found between group and toy condition.

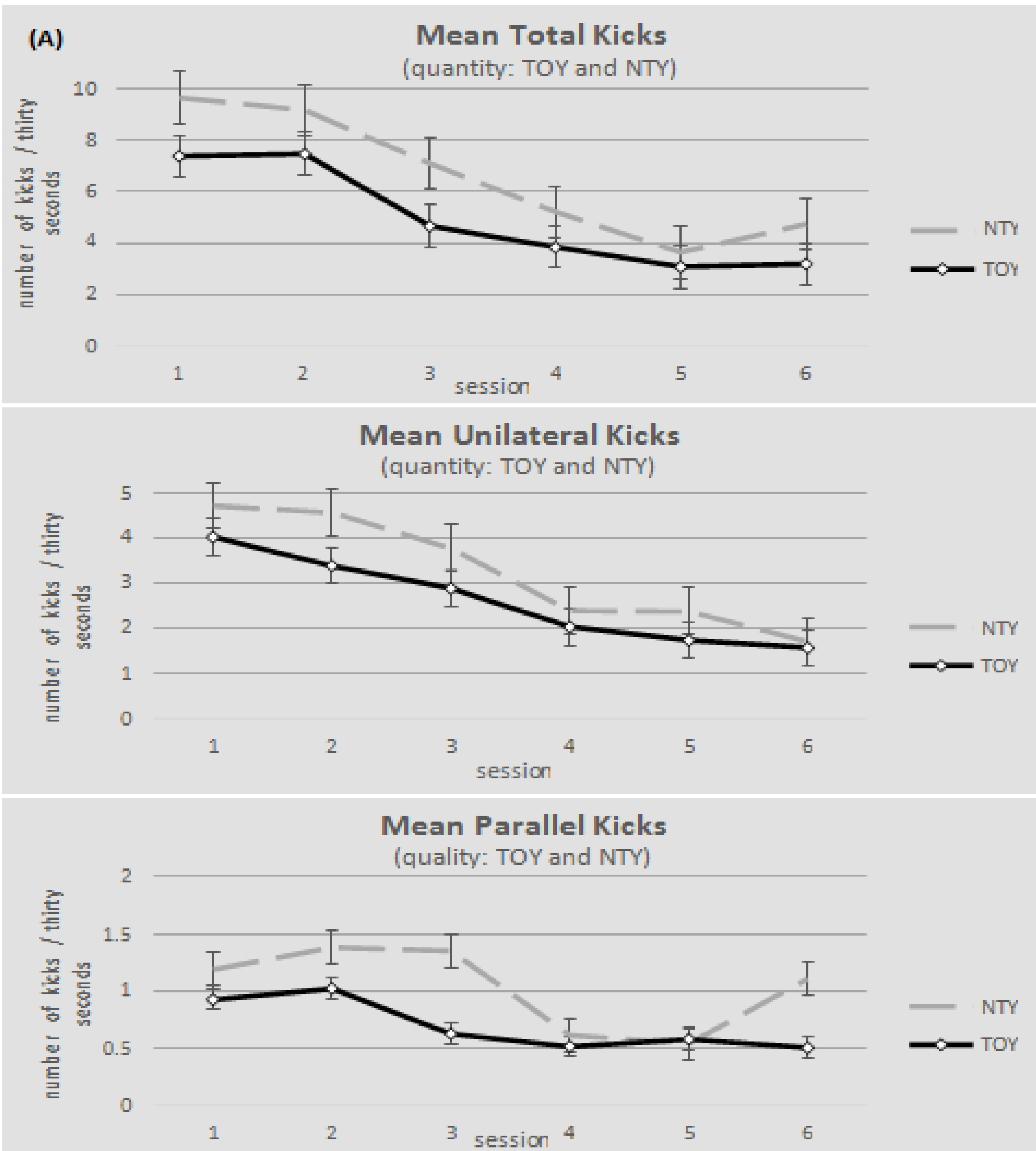


Figure 3. Kicking rate for TOY and NTY conditions for (A) total kicks; (B) unilateral kicks; (C) parallel kicks. *Note*: TOY: Toy condition; NTY: No Toy condition. One session = two weeks.

Discussion Early identification of developmental deficits in infants with PS is critical to facilitating earlier diagnosis, treatment, and better outcomes. Current clinical measures of motor development are limited and fail to identify deficits until 1-2 years after the brain lesion occurs, well after infants may be eligible to begin therapy. The purpose of this study was to examine the role of spontaneous kick quantity and quality in differentiating cerebral palsy in infants with perinatal stroke and to determine kicking performance with and without toys.

Our first hypothesis stated that infants with PS that would go on to develop cerebral palsy (infants denoted CP) would show differences in kick quantity and quality when compared to TD infants and PS infants who would not develop cerebral palsy (infants denoted PS_n). Our hypothesis was partially supported. Kicking trajectories, defined as the changes in a group's mean kick frequency over time, were examined. As a group, infants with CP showed a significant interaction in quantitative measures total and unilateral kicks and quality measure alternating kicks with both TD and PS_n infants. Furthermore, TD and PS_n infants showed no significant interactions or effect of group. These results indicate that as a group, CP infants exhibit kicking trajectories that are statistically distinct from their peers without cerebral palsy. Examination of the graphs shows that while TD and PS_n infants steadily decreased their kicks over time after session 2, CP infants appear to increase their kicking and exhibit two peaks at sessions 2 and 5. Previous studies have suggested that infants who sustain high frequencies of kicking exhibit delayed walking (Jeng et al., 2004; Smith et al., 2015).

The failure to attain common motor milestones such as crawling, walking, and running at appropriate ages is considered a diagnostic criterion for cerebral palsy. Age of walking was not followed in this study, but it is probable that the CP group walked at later ages than their PS_n peers. This speculation needs to be followed up by further study. Overall, the CP group appears to show a significant difference in the trajectory of quantitative measures of spontaneous kicking, especially after session 3, or about 15 weeks of age. In terms of kick quality, previous studies have suggested that alternating kicks, our designated "least mature" kick type, are typically found in high frequency in younger and disabled infants. It is for alternating kicks that we see the clearest rise in CP kick frequency. At session 5, CP infants kick alternately at a frequency of 10 kicks/minute greater than their typical peers, higher than in any other session or group throughout the study. However, no differences or effects of time were found for the second measure of quality, parallel kicks. We conclude that parallel kicks are not a useful measure for distinction in infants with stroke. By itself, alternating kicks provide an incomplete measure of kick quality but appear to reveal clear differences in infants with cerebral palsy from peers without.

The greatest limitation on this project is the low power for the CP group. With *n*=3 and large variability in kicking rates, it is difficult to make sweeping conclusions about all infants with stroke who will go on to develop cerebral palsy. However, the CP group showed a marked departure from the typically developing cohorts in a direction that previous studies have suggested is indicative of motor deficits. While there does appear to be a difference in number of peaks seen, i.e. TD ad PSn infants show 1 peak while CP show 2, we believe the fact that CP infants increased their kicking after session 3 is most relevant. It appears that in the time frame during which infants without cerebral are decreasing their kicking in order to advance to other movements such as self-exploration and rolling over, the CP infants remain in kicking stage.

A theoretical explanation to delayed or sustained kicking may be found in the fact that early spontaneous movements have been attributed to the existence of central pattern generators, or neuronal networks carrying the information necessary for complex movement (Barlowe & Estep 2006). It is hypothesized that these generators fire tens of thousands of times in early life in order to prime muscle groups for the sophisticated orchestration needed for walking, grasping, etc. If these neural networks are damaged, a longer period may be required to reach sufficiency in spontaneous kicking (if reached at all) and more complex movements may be difficult to attain. In this project we did not examine brain imaging and thus further study will be needed to explore the relationship between neural networks and spontaneous kicking. However, it is known that failure to reach motor milestones by a certain age tends to result in motor delays and lifelong deficits. This time period coincides with the time during which approximately half of newly generated neurons will be eliminated (Hadders-Algra 2004). This points to the existence of a “sensitive period” during which, similar to language acquisition, certain movements must be developed for proper use and coordination later in life. With damaged neural networks, CP infants may be unable to achieve competency during this period on their own. Early intervention has been proven to facilitate better outcomes in young children with other neurodevelopmental disorders, and we propose that infants at risk for cerebral palsy are no different.

Our second hypothesis stated that the toy condition will elicit greater kicking quantity and quality than the no toy condition. It was proven to be false and actually the opposite of what our data suggested. Across groups, the no toy condition was found to produce a significantly different number of total and unilateral kicks (quantity measures) and a trend for parallel kicks (a quality measure). Examination of the graphs showed that the no toy condition actually produced more kicks in all areas, as opposed to less. No interaction between time and toy status was found, indicating that the no toy condition did not inherently change the kick trajectories: it simply produced more of the same kicks.

Our reasoning for this hypothesis was based on the fact that toys are universally used in clinical practice to attract and engage infants. Many common clinical examinations, most notably the Bayley Scales of Motor Development, rely on toys as integral components of the test. Additionally, previous studies with spontaneous kicking have shown that a suspended mobile is capable of eliciting significantly higher rates of kicking when compared to no intervention (Lindsley 1963). Thus, we hypothesized that the toys used in our experiment would have a similar effect. The mobile paradigm setup described above was not appropriate for this study as the degree of kicking enhancement has been theorized to be a function of an infant's cognition, and it is regularly used to measure infant cognition rather than simple motor ability (Chen et al., 2015). Our protocol called to place the toy directly into the infant's hand so that the infant would hold and interact with the toy. Our thought process was that doing so would place the infant in a state of increased engagement and excitement, which is known to also increase kicking. The placement of the toy in the infants' hands may have encouraged upper extremity movements or passive exploration of the toy at the expense of kicking. There was little opportunity for the lower extremities to interact with the toy. The manner in which we introduced the toys resulted in a significant reduction in kick quantity and quality.

Conclusion Currently there are no studies examining the relationship between spontaneous kicking and development of cerebral palsy. Clinical practice fails to identify infants with cerebral palsy in a timely manner to facilitate early intervention strategies and produce the best outcomes. Our findings suggest that repeated spontaneous kicking assessment, especially beginning at 15 weeks of age, may assist in identifying infants with cerebral palsy at much younger ages than is currently possible. When paired with other early diagnostic measures such as cranial imaging, neurological assessment, and general movements assessment, a test battery may be developed to identify infants exhibiting early signs of motor deficits (Vries et al., 2011; Guzzetta 2003). When implementing these tests we caution the use of toys in lower extremity analyses. While the literature suggests that toys are a critical component to upper extremity function, learning, and exploration, our findings suggest that toys in the hands has a spillover effect to the legs, reducing spontaneous kicking for all infants. Since infants with CP kick more than their TD counterparts, providing earlier exposure to toys may provide a beneficial enhanced environment for promotion of normalization of kicking movements.

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